BIO NEWS

April, 2018

In-Vivo Science International Inc.

1230 Bordeaux Drive

Sunnyvale, CA 94089, USA

目次

2018 年 3 月のニュース

＝研究編（詳細については各番号をクリックして下さい)＝

2018 年 3 月のニュース

＝企業関連ニュース他＝

・第一三共、Exelixis との提携で見つけた降圧薬 Esaxerenone を日本に承認申請（2/28）
・AstraZeneca の化合物 6 つを受け継ぐ自己免疫疾患治療開発新会社 Viela Bio が最大 2 億 5,000 万ドル（$250 million）を元手に発足（3/1）
・Novartis 中国の抗癌剤開発リーダーBin Peng 氏が上海の EpimAb の最高医学責任者に就任（3/1）
・iPS の臨床研究 阪大が了承（3/1）
・武田薬品、TiGenex 買収に続いてアイルランドに幹細胞製造工場を作る（3/2）
・Mylan が Revance と組んで、Allergan の旗艦薬 BOTOX（ボツリヌス毒素）の安価なバイオシミラーを共同開発（3/2）
・失明マウス、ヒト由来の細胞移植で光に反応 -理研チーム（3/4）
・南ア・リステリア流行の発生元が明らかに (3/5)
・人への臓器移植用ブタ作製、来年初めにも供給 -明治大、京都府大など (3/5)
・電子タバコ使用 10 代若者の尿からより高レベルの発癌性物質が検出された（3/6）
・てんかんの原因、遺伝子変異発見…東大など研究チーム (3/6)
・安価な iPS 培養法 京大が開発（3/6）
・体外処理不要の体内遺伝子治療の Homology が最大 1 億ドルの IPO 調達を計画（3/6）
・電子タバコ使用 10 代若者の尿からより高レベルの発癌性物質検出（3/6）
・大日本住友製薬、小児の双極性うつ病の LATUDA 治療を FDA が承認（3/7）
・PAREXEL、INC Research を率いていた Jamie Macdonald 氏を CEO に任命（3/7）
・英国が EU 離脱後も欧州医薬品庁の一員であり続ける取り決めを検討（3/7）
・23andMe の癌の遺伝子検査結果を顧客に届けることを FDA が初めて承認（3/7）
・Novartis、Science 37 社との提携拡大～拠点がほぼ不要のバーチャル試験を目指す（3/8）
・75%の水で育つ植物を開発 -米イリノイ大学（3/8）
・米国のバイオシミラー普及を妨げる不正契約への対策を講じると FDA 長官が表明（3/9）
・人工知能（AI）企業 Atomwise が Monsanto Growth Ventures, DCVC (Data Collective), B Capital Group 主導の 4,500 万ドル（$45 million）の投資を獲得（3/9）
・米国成人の 1 日のナトリウム平均摂取量は約 4g～24 時間採尿結果に基づく（3/10）
・中国一人っ子政策緩和で帝王切開が着実に減少（3/11）

・Eisai、Merck とレンビマの共同開発契約を締結（3/12)
・Gilead に 30 年近く勤務する R&D 長/最高科学責任者・Norbert Bischofberger 氏が辞任（3/13)
・肥満薬 Contrave の Orexigen Therapeutics が破産（3/13)
・プラスチック海洋汚染、小型動物性プランクトンのオキアミが奥の手となる可能性 豪研究 (3/13)
・GSK の元 CEO・Andrew Witty 氏が UnitedHealth の薬剤給付事業を率いる（3/14)
・Boehringer、バンダービルト大学と組んで MCL1 発現癌の治療薬発見（3/16)
・米国の薬物乱用による死亡率は 1980 年から 2014 年に 618%上昇（3/16)
・コーヒー豆成分クロロゲン酸 認知機能を改善 -米沢栄養大（3/16)
・Pfizer が昇給と 800 万ドル相当のボーナスを CEO・Ian Read に約束して 1 年間の引き留め (3/19)
・大製薬会社としては初の医療用大麻製品販売に向けた合意、Novartis (3/20)
・自傷した 10 代若者はその後 1 年間に 50 倍近く自殺しやすい（3/20)
・老化細胞除去治療の UNITY Biotechnology が 5,500 万ドル調達（3/20)
・重度外傷性脳損傷小児は後に ADHD を発症しやすい (3/21)
・米国の 1 年あたりの HIV 感染者数が 2015 年までの 8 年間に約 15%減少（3/21)
・人工知能創薬企業 twoXAR が 1,000 万ドル調達（3/21)
・AstraZeneca がロイヤルティ支払いを拒否していると Array が訴え（3/21)
・天皇陛下執筆の魚類図鑑刊行（3/22)
・Shire、EURORDIS や Microsoft と組んで希少疾患診断の妨げの解消を目指す（3/23)
・気管支ぜんそく 原因を解明 -東北大（3/23)
・GSK、帯状疱疹ワクチン Shingrix が 2 つの重要市場・欧州と日本で承認された（3/23)
・初期胃癌切除患者のピロリ菌除去治療で後の胃癌発現が減少（3/24)
・Pfizer の OTC 事業の競売から Reckitt も GlaxoSmithKline も脱落（3/24)
・宇宙望遠鏡技術でがん顕微鏡 -JAXA など (3/27)
・理研 生命科学 3 機関を 4 月統合（3/27)
・米国成人の肥満は依然として増えていて 4 割が肥満～若者は横ばいで 18.5%（3/27)
・シンガポールの抗癌剤開発会社 ASLAN が 8,600 万ドルの IPO 調達を計画（3/28)
・武田薬品が Shire を買う検討をしている（3/29)

・体外処理不要の体内遺伝子治療の Homology が 1 億 4,400 万ドルの IPO 調達達成 (3/30)

目次に戻る

1．皮膚細菌が皮膚癌から保護 -マウス実験

2018 年 3 月 1 日

カリフォルニア大学サンディエゴ校医学部の研究者らが 2 月 28 日に *Science Advances* 誌に発表した研究で、皮膚に対する細菌の潜在的な新しい役割が報告されている。
これによると、健康なヒトの皮膚に共通する表皮ブドウ球菌（Staphylococcus epidermidis）株は、いくつかの癌の増殖を選択的に抑制する能力を発揮するとしており、この独特な皮膚細菌が、いくつかの種類の癌細胞を死滅させるが、正常細胞には毒性がないように見える化学物質を産生することを示している。
チームは S. epidermidis 株が化学化合物 6-N-ヒドロキシアミノプリン（6-HAP）を産生することを発見、6-HAP を産生しない皮膚上の表皮ブドウ球菌を有するマウスは、癌を引き起こす紫外線（UV）に曝露された後に多くの皮膚腫瘍を有したが、6-HAP を産生する表皮ブドウ球菌を有するマウスでは皮膚腫瘍はできなかった、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/03/180301103701.htm

---

Beneficial skin bacteria protect against skin cancer

Date:

March 1, 2018

Source:

University of California - San Diego

Summary:

Science continues to peel away layers of the skin microbiome to reveal its protective properties. Researchers now report on a potential new role for some bacteria on the skin: protecting against cancer.

FULL STORY

This is S. epidermidis growing on an agar plate. A strain of S. epidermidis was shown to produce a molecule that kills cancer cells and inhibits the development of skin tumors on mice. UC San Diego Health

Science continues to peel away layers of the skin microbiome to reveal its protective properties. In a study published in *Science Advances* on February 28, University of California San Diego School of Medicine researchers report a potential new role for some bacteria on the skin: protecting against cancer.

"We have identified a strain of *Staphylococcus epidermidis*, common on healthy human skin, that exerts a selective ability to inhibit the growth of some cancers," said Richard Gallo, MD, PhD,

Distinguished Professor and chair of the Department of Dermatology at UC San Diego School of Medicine. "This unique strain of skin bacteria produces a chemical that kills several types of cancer cells but does not appear to be toxic to normal cells."

The team discovered the *S. epidermidis* strain produces the chemical compound 6-N-hydroxyaminopurine (6-HAP). Mice with *S. epidermidis* on their skin that did not make 6-HAP had many skin tumors after being exposed to cancer-causing ultraviolet rays (UV), but mice with the *S. epidermidis* strain producing 6-HAP did not.

6-HAP is a molecule that impairs the creation of DNA, known as DNA synthesis, and prevents the spread of transformed tumor cells as well as the potential to suppress development of UV-induced skin tumors.

Mice that received intravenous injections of 6-HAP every 48 hours over a two-week period experienced no apparent toxic effects, but when transplanted with melanoma cells, their tumor size was suppressed by more than 50 percent compared to controls.

"There is increasing evidence that the skin microbiome is an important element of human health. In fact, we previously reported that some bacteria on our skin produce antimicrobial peptides that defend against pathogenic bacteria such as, *Staph aureus*," said Gallo.

In the case of *S. epidermidis*, it appears to also be adding a layer of protection against some forms of cancer, said Gallo. Further studies are needed to understand how 6-HAP is produced, if it can be used for prevention of cancer or if loss of 6-HAP increases cancer risk, said Gallo.

More than 1 million cases of skin cancer are diagnosed in the United States each year. More than 95 percent of these are non-melanoma skin cancer, which is typically caused by overexposure to the sun's UV rays. Melanoma is the most serious form of skin cancer that starts in the pigment-producing skin cells, called melanocytes.

Story Source:

Materials provided by **University of California - San Diego**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Teruaki Nakatsuji, Tiffany H. Chen, Anna M. Butcher, Lynnie L. Trzoss, Sang-Jip Nam, Karina T. Shirakawa, Wei Zhou, Julia Oh, Michael Otto, William Fenical, Richard L. Gallo. **A commensal strain of Staphylococcus epidermidis protects against skin neoplasia**. *Science Advances*, 2018; 4 (2): eaao4502 DOI: 10.1126/sciadv.aao4502

Cite This Page:

- MLA
- APA
- Chicago

University of California - San Diego. "Beneficial skin bacteria protect against skin cancer." ScienceDaily. ScienceDaily, 1 March 2018. <www.sciencedaily.com/releases/2018/03/180301103701.htm>.

目次に戻る

2. 加齢による脳の悪化に寄与する遺伝子 -マウス実験

2018 年 3 月 5 日

英国ケンブリッジの Babraham Institute とイタリアローマの Sapienza 大学の科学者グループによって、加齢による脳の悪化を促す遺伝子および遺伝的スイッチが同定された。
3 月 5 日に *Aging Cell* 誌で発表されたこの研究によると、Dbx2 と呼ばれる遺伝子の 1 つに起きる変化が脳幹細胞を早期に老化させ、それが原因で脳がゆっくり悪化する、としている。
研究者らは、若いマウスの脳幹細胞内で Dbx2 の活性度を上げることにより、これらの幹細胞が古い細胞のように振る舞い、脳幹細胞の増殖を遅らせることを示した。また、加齢によって古くなった幹細胞におけるいくつかのエピジェネティックマーク（遺伝子スイッチの一種）の変化を明らかにした。このマークは、特定の遺伝子活性に影響するゲノムに付けられた化学タグであり、このマークの配置が細胞の挙動を変化させる。
研究者らの目標は、古い細胞の時計を元に戻すことであり、これがマウスでできれば、同じことが人間に対しても可能はずだ、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/03/180305093626.htm

---

Genes for age-linked brain deterioration identified

Date:

March 5, 2018

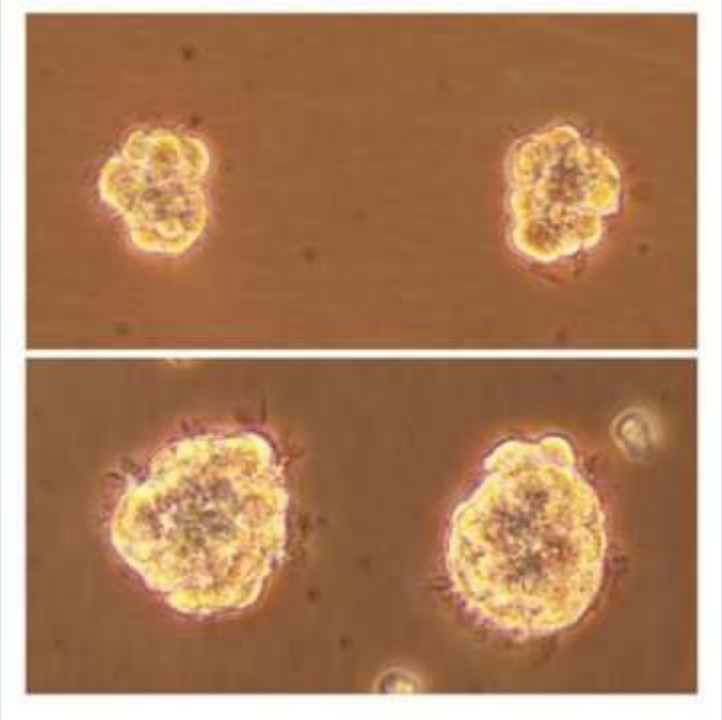
Source:

Babraham Institute

Summary:

A group of genes and genetic switches involved in age-related brain deterioration have been identified. The research found that changes to one of these genes, called Dbx2, could prematurely age brain stem cells, causing them to grow more slowly.

FULL STORY



Spheres of mouse neural stem cells grown in the lab. Cells in the upper image are from older mice and produce smaller spheres due to the deterioration in neural stem cell growth.

Credit: Dr. Giuseppe Lupo

A group of genes and genetic switches involved in age-related brain deterioration have been identified by scientists at the Babraham Institute, Cambridge and Sapienza University, Rome. The research, published online today (5th March) in Aging Cell, found that changes to one of these genes, called Dbx2, could prematurely age brain stem cells, causing them to grow

more slowly. The study was led jointly by Giuseppe Lupo and Emanuele Cacci in Italy and Peter Rugg-Gunn in the UK.

Cells in the brain are constantly dying and being replaced with new ones produced by brain stem cells. As we age, it becomes harder for these stem cells to produce new brain cells and so the brain slowly deteriorates. By comparing the genetic activity in brain cells from old and young mice, the scientists identified over 250 genes that changed their level of activity with age. Older cells turn some genes, including Dbx2, on and they turn other genes off.

By increasing the activity of Dbx2 in young brain stem cells, the team were able to make them behave more like older cells. Changes to the activity of this one gene slowed the growth of brain stem cells. These prematurely aged stem cells are not the same as old stem cells but have many key similarities. This means that many of the genes identified in this study are likely to have important roles in brain ageing.

The research also identified changes in several epigenetic marks -- a type of genetic switch -- in the older stem cells that might contribute to their deterioration with age. Epigenetic marks are chemical tags attached to the genome that affect the activity of certain genes. The placement of these marks in the genome change as we age and this alters how the cells behave. The researchers think that some of these changes that happen in the brain may alter causing brain stem cells to grow more slowly.

First author on the paper, Dr Giuseppe Lupo, Assistant Professor at Sapienza University said: "The genes and gene regulators that we identified are corrupted in neural stem cells from older mice. By studying the Dbx2 gene we have shown that these changes may contribute to ageing in the brain by slowing the growth of brain stem cells and by switching on the activity of other age-associated genes."

Co-lead scientist Dr Peter Rugg-Gunn at the Babraham Institute said: "Ageing ultimately affects all of us and the societal and healthcare burden of neurodegenerative diseases is enormous. By understanding how ageing affects the brain, at least in mice, we hope to identify ways to spot neural stem cell decline. Eventually, we may find ways to slow or even reverse brain deterioration -- potentially by resetting the epigenetic switches -- helping more of us to stay mentally agile for longer into old age."

Co-lead scientist Dr Emanuele Cacci at Sapienza University said: "We hope this research will lead to benefits for human health. We have succeeded in accelerating parts of the ageing process in neural stem cells. By studying these genes more closely, we now plan to try turning back the clock for older cells. If we can do this in mice, then the same thing could also be possible for humans."

Story Source:

Materials provided by **Babraham Institute**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Giuseppe Lupo, Paola S. Nisi, Pilar Esteve, Yu-Lee Paul, Clara Lopes Novo, Ben Sidders, Muhammad A. Khan, Stefano Biagioni, Hai-Kun Liu, Paola Bovolenta, Emanuele Cacci, Peter J. Rugg-Gunn. **Molecular profiling of aged neural progenitors identifies Dbx2 as a candidate regulator of age-associated neurogenic decline**. *Aging Cell*, 2018; e12745 DOI: 10.1111/acel.12745

Cite This Page:

- MLA
- APA
- Chicago

Babraham Institute. "Genes for age-linked brain deterioration identified." ScienceDaily. ScienceDaily, 5 March 2018. <www.sciencedaily.com/releases/2018/03/180305093626.htm>.

目次に戻る

3. 家族性ヒトプリオン病の伝搬リスク -マウス実験

2018 年 3 月 8 日

プリオン病は、通常は無害なプリオンタンパク質が異常になって人体および脳のクラスターやフィラメントに集まる時に発生するが、このプロセスの原因は完全には理解されていない。家族性ヒトプリオン病は家族内で伝搬し、遺伝的クロイツフェルト・ヤコブ病などがこれに属す。34 種類のプリオンタンパク質突然変異と関連しているとされているが、これら既知の 34 種類のうち、現在伝搬能力について 13 が試験され、9 つでサルまたはマウスにおいて伝搬可能であることが示されている。
今回、国立衛生研究所（NHI）の一部、国立アレルギー・感染症研究所の科学者らが、まだ研究されていない突然変異の 3 種類について、家族性プリオン病で死亡した 3 人の脳のサンプルを実験用マウスに施して、これらの突然変異が伝搬可能か判定した。
その結果、Y226X と G131V の 2 つについて、伝搬可能（透過性）であることが判明した、として、*Acta Neuropathologica Communications* 誌に発表されている。

英文記事：
https://www.sciencedaily.com/releases/2018/03/180308120549.htm

---

Transmission risk of familial human prion diseases to mice

Date:

March 8, 2018

Source:

NIH/National Institute of Allergy and Infectious Diseases

Summary:

Familial human prion diseases are passed within families and are associated with 34 known prion protein mutations. To determine whether three of the unstudied mutations are transmissible, scientists exposed research mice to brain samples from three people who died from a familial prion disease. After observing the mice for about two years, they found two of the mutations, Y226X and G131V, are transmissible.

FULL STORY

Familial human prion diseases are passed within families and are associated with 34 known prion protein mutations. To determine whether three of the unstudied mutations are transmissible, scientists from the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, exposed research mice to brain samples from three people who died from a familial prion disease. After observing the mice for about two years, they found two of the mutations, Y226X and G131V, are transmissible.

Perhaps more interesting, the Y226X patient sample had previously been preserved in formaldehyde for three days, embedded in wax, and dried on glass specimen slides for several years before being rehydrated for the study. Yet, the sample infected four of eight mice.

The finding illustrates the hardiness of prion infectivity and the potential risks associated with prion transmission, potentially through surgery, blood transfusion or tissue donation. Samples for the other two mutations studied were taken from frozen brain tissue that was thawed.

Prion diseases originate when normally harmless prion protein molecules become abnormal and gather in clusters and filaments in the human body and brain. The reasons for this process are not fully understood. Familial human prion diseases include genetic Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease, and fatal familial insomnia. All are fatal and thus far untreatable. Of the 34 known prion protein mutations, scientists now have tested 13 for transmissibility, identifying nine as transmissible to monkeys or mice.

Story Source:

Materials provided by **NIH/National Institute of Allergy and Infectious Diseases**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Brent Race, Katie Williams, Andrew G. Hughson, Casper Jansen, Piero Parchi, Annemieke J. M. Rozemuller, Bruce Chesebro. **Familial human prion diseases associated with prion protein mutations Y226X and G131V are transmissible to transgenic mice expressing human prion protein**. *Acta Neuropathologica Communications*, 2018; 6 (1) DOI: 10.1186/s40478-018-0516-2

Cite This Page:

- MLA
- APA
- Chicago

NIH/National Institute of Allergy and Infectious Diseases. "Transmission risk of familial human prion diseases to mice." ScienceDaily. ScienceDaily, 8 March 2018. <www.sciencedaily.com/releases/2018/03/180308120549.htm>.

目次に戻る

４．三次喫煙がマウスの肺癌リスクを高める

2018 年 3 月 9 日

エネルギー省のローレンス バークレー国立研究所（バークレー研究所）の研究者らは、2017 年に初めて、喫煙がされなくなってからも屋内の表面や埃の中に長く残る毒性残留物を確認し、これらが間接喫煙として若年マウスの低体重や免疫変化と関連していることを報告した。彼らが最近 *Clinical Science* 誌で発表したフォローアップ研究では、早期の間接喫煙がマウスの肺癌の発生率と重症度上昇にも関連していることを示している。
バークレー研究所のこの研究では、4 週齢から 7 週齢までの A/J マウスに、人間の幼児の曝露摂取に匹敵する、体重 1 キログラム当たり約 77 マイクログラムと推定される量を三次喫煙になるように含浸した布と一緒に飼育したところ、40 週間後に肺癌（腺癌）、腫瘍のサイズや数、全てにおいて発生率の増加が見られた、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/03/180309095539.htm

---

Third-hand smoke found to increase lung cancer risk in mice

Date:

March 9, 2018

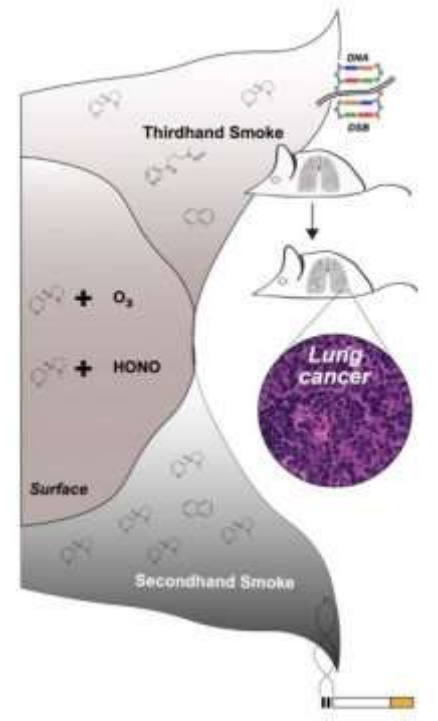
Source:

DOE/Lawrence Berkeley National Laboratory

Summary:

Researchers have identified third-hand smoke, the toxic residues that linger on indoor surfaces and in dust long after a cigarette has been extinguished, as a health hazard nearly 10 years ago. Now a new study has found that it also increases lung cancer risk in mice.

FULL STORY



Thirdhand smoke contains the chemicals in secondhand smoke from a cigarette that are deposited on indoor surfaces. Some of these chemicals interact with molecules from the air to create a toxic mix that includes potentially cancer-causing compounds. These compounds induce double-stranded breaks (DSBs) in DNA, which if not repaired correctly, could lead to tumorigenesis in mice. In this study, the researchers have shown for the first time that thirdhand smoke exposure induces lung cancer in A/J mice in early life.

Credit: Antoine Snijders, Jian-Hua Mao, and Bo Hang/Berkeley Lab

Researchers at the Department of Energy's Lawrence Berkeley National Laboratory (Berkeley Lab) identified thirdhand smoke, the toxic residues

that linger on indoor surfaces and in dust long after a cigarette has been extinguished, as a health hazard nearly 10 years ago. Now a new study has found that it also increases lung cancer risk in mice.

A team led by Antoine Snijders, Jian-Hua Mao, and Bo Hang of Berkeley Lab first reported in 2017 that brief exposure to thirdhand smoke is associated with low body weight and immune changes in juvenile mice. In a follow-up study published recently in *Clinical Science*, the researchers and their team have determined that early thirdhand smoke exposure is also associated with increased incidence and severity of lung cancer in mice.

Field studies in the U.S. and China have confirmed that the presence of thirdhand smoke in indoor environments is widespread, and traditional cleaning methods are not effective at removing it. Because exposure to thirdhand smoke can occur via inhalation, ingestion, or uptake through the skin, young children who crawl and put objects in their mouths are more likely to come in contact with contaminated surfaces, and are therefore the most vulnerable to thirdhand smoke's harmful effects.

In the Berkeley Lab researchers' new study, an experimental cohort of 24 A/J mice (a strain susceptible to spontaneous lung cancer development) was housed with scraps of fabric impregnated with thirdhand smoke from the age of 4 weeks to 7 weeks. The dose the mice received was estimated to be about 77 micrograms per kilogram of body weight per day -- comparable to the ingestion exposure of a human toddler living in a home with smokers. Forty weeks after the last exposure, these mice were found to have an increased incidence of lung cancer (adenocarcinoma), larger tumors, and a greater number of tumors, compared to 19 control mice.

Their work also sheds light on what happens on both a molecular and cellular level. If thirdhand smoke toxins damage DNA within cells and the damage is not repaired properly, it can give rise to mutations, which may lead to the cell becoming cancerous. To further investigate how thirdhand smoke exposure promotes tumor formation, the team performed in vitro studies using cultured human lung cancer cells.

These studies indicated that thirdhand smoke exposure induced DNA double-strand breaks and increased cell proliferation and colony formation. In addition, RNA sequencing analysis revealed that thirdhand smoke exposure caused endoplasmic reticulum stress and activated p53 (tumor suppressor) signaling. The physiological, cellular, and molecular data indicate that early exposure to thirdhand smoke is associated with increased lung cancer risk.

Story Source:

Materials provided by **DOE/Lawrence Berkeley National Laboratory**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Hilary D. Marston, Catharine I. Paules, Anthony S. Fauci. **Monoclonal Antibodies for Emerging Infectious Diseases — Borrowing from History**. *New England Journal of Medicine*, 2018; DOI: 10.1056/NEJMp1802256

Cite This Page:

- MLA
- APA
- Chicago

DOE/Lawrence Berkeley National Laboratory. "Third-hand smoke found to increase lung cancer risk in mice." ScienceDaily. ScienceDaily, 9 March 2018. <www.sciencedaily.com/releases/2018/03/180309095539.htm>.

目次に戻る

5．マウスはヒトに飼い慣らされると外観が変わる

2018 年 3 月 16 日

動物が飼い慣らされると、野生種に比べてその外観が変化する。家畜のウサギ、犬、ブタ、全てに見られる白い斑点、だらりとした耳、脳の縮小、鼻の短縮などが良い例で、科学ではこれを家畜症候群と呼んでいる。
今回スイスのチューリッヒ大学（UZH）の進化生物学者らは、野生動物のマウス（Mus musculus domesticus）が人間に飼い慣らされた結果、これらと同様に外観に変化をもたらすことを初めて示した。
この研究は *Royal Society Open Science* 誌に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2018/03/180316113053.htm

---

Mice change their appearance as a result of frequent exposure to humans

Date:

March 16, 2018

Source:

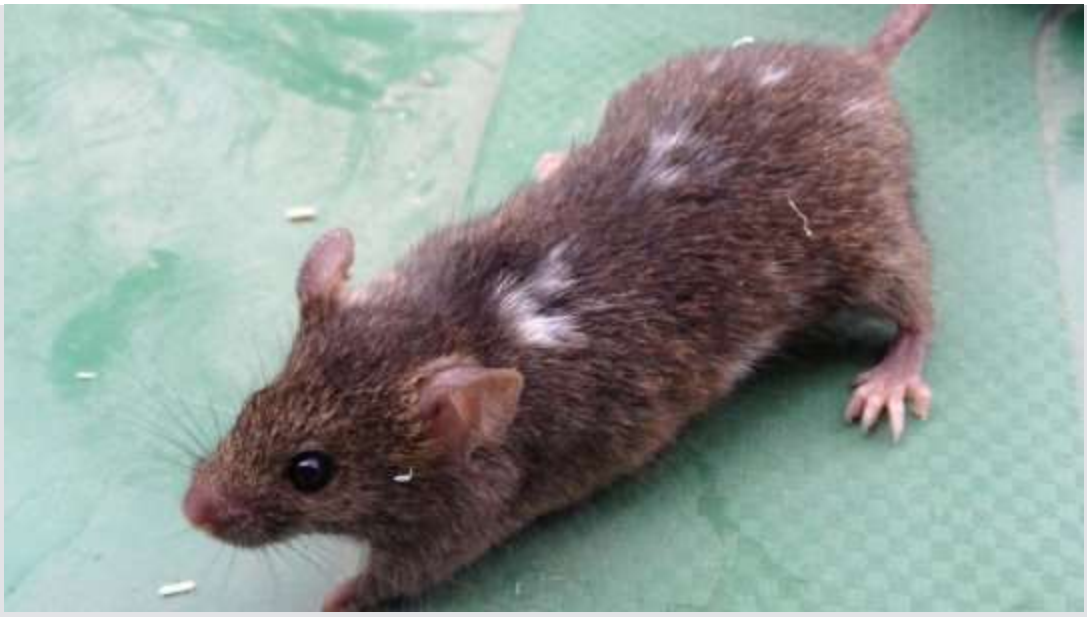
University of Zurich

Summary:

Many tame domesticated animals have a different appearance compared to their relatives in the wild, for example white patches in their fur or shorter snouts. Researchers have now

for the first time shown that wild house mice develop the same visible changes -- without selection, as a result of exposure to humans alone.

FULL STORY



The white patches in the brown fur of the house mice are a sign of self-domestication.

Credit: Linda Heeb

Dogs, cows, sheep, horses, pigs, and birds -- over the past 15,000 years, our ancestors domesticated dozens of wild animals to keep them as farm animals or pets. To make wild wolves evolve into tame dogs, the least aggressive animals, or most gentle ones, were selected for breeding. Tameness was therefore the key criterion for selection. Over time, it wasn't only the animals' behavior that changed, but their appearance as well -- with the same changes emerging across various species. For example, domestic rabbits, dogs, and pigs all have white patches, floppy ears, smaller brains, and shorter snouts. In science, this suite of traits is referred to as the domestication syndrome.

Regular exposure to humans results in white patches in the fur

A team of researchers led by Anna Lindholm from the Department of Evolutionary Biology and Environmental Studies at UZH has now also observed this phenomenon in wild mice (*Mus musculus domesticus*) that live in a barn near Zurich. Within a decade, this population of mice developed two of the distinct phenotypic changes: white patches in their otherwise brown-colored fur as well as shorter snouts. "The mice gradually lost their fear and developed signs of domestication. This happened without any human selection, solely as a result of being exposed to us regularly," says Anna Lindholm. The evolutionary biologist has been studying the mice that live in the empty barn for about 15 years. These animals are regularly provided with food and water, and investigated by the researchers.

Experimental taming of wild foxes provides the key

Scientists' knowledge about the domestication syndrome comes from a remarkable experiment that began in Siberia in 1959. Soviet geneticist Dmitry Belyaev tamed wild foxes and investigated their evolutionary changes. He selected the tamest animals from among every new generation. Over time, the foxes began to change their behavior: They not only tolerated people, but were outright friendly. At the same time, their appearance also changed: Their fur featured white patches, their snouts got shorter, their ears drooped, and their tails turned curly.

Neural crest stem cells provide link

It appears that a small group of stem cells in the early embryo -- the neural crest -- is responsible for these behavioral and physical changes that take place in parallel. The ear's cartilage, the teeth's dentine, the melanocytes responsible for the skin's pigmentation, as well as the adrenal glands which produce stress hormones are all derived from these stem cells. The selection of less timid or aggressive animals results in smaller adrenal glands that are less active, and therefore leads to tamer animals. Changes in the color of fur and head size can thus be considered unintended side effects of domestication, as these traits can also be traced back to stem cells in the neural crest that were more passive in the early stages of development.

How wild mice became tame without selection

The observations of the study's first author Madeleine Geiger increases the understanding of how house mice began to live in closer proximity to humans, attracted by their food, some 15,000 years

ago. As a result of this proximity alone, the rodents got used to people and became tamer. "This self-domestication resulted in the gradual changing of their appearance -- incidentally and inadvertently," says Geiger. Evolutionary biologists assume that the development from wild wolf to domestic dog also initially began without the active involvement of humans. Wolves that lived near humans became less timid and aggressive -- the first step in becoming domesticated.

Story Source:

Materials provided by **University of Zurich**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Madeleine Geiger, Marcelo R. Sánchez-Villagra, Anna K. Lindholm. **A longitudinal study of phenotypic changes in early domestication of house mice**. *Royal Society Open Science*, 2018; 5 (3): 172099 DOI: 10.1098/rsos.172099

Cite This Page:

- MLA
- APA
- Chicago

University of Zurich. "Mice change their appearance as a result of frequent exposure to humans." ScienceDaily. ScienceDaily, 16 March 2018. <www.sciencedaily.com/releases/2018/03/180316113053.htm>.

目次に戻る

6. 細胞が時間を伝えるのに不可欠な遺伝子 -マウス実験

2018 年 3 月 19 日

概日リズムは光に敏感なほとんど全ての生物に見られる。ヒトの概日リズムの問題は、高血圧、代謝障害、不眠症といった疾患に関連し、シフト労働者や高齢者らは概日時計の混乱によってこれらの疾患リスクが増加するとされている。
今回米国科学アカデミー紀要に発表された、東京大学を中心とした研究チームによる新たな研究では、この概日リズムが細胞ストレスと直接関連している可能性があることが初めて明らかにされている。
研究者らは、アポトーシスシグナル調節キナーゼ 1、2、3（Ask1、Ask2、Ask3）の 3 つの遺伝子を欠く細胞およびマウスを作成。Ask 遺伝子を持たない細胞は、塩分濃度が高過ぎたり低過ぎたりした環境では正常細胞が増殖することから期待される概日リズムには変化が見られなかった。また、細胞があまりにも多くの酸化ストレスを蓄積したあとに予想される変化に対しても不浸透性であった。この制御されない酸化的ストレスが化学的バランスの変化のために細胞内に潜在的な毒素を作り出す。
研究チームは、Ask 遺伝子を酸化的ストレスに関連付ける詳細な細胞メカニズムと概日リズムに影響を与える潜在的方法について更に研究を続ける、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/03/180319215709.htm

---

Three genes essential for cells to tell time

Date:

March 19, 2018

Source:

University of Tokyo

Summary:

One family of genes allows cells to adapt to daily changes in environmental conditions by adjusting their internal 'body clock,' the circadian clock responsible for regular sleep-wake cycles. The new discovery reveals for the first time that circadian regulation may be directly connected to cellular stress.

FULL STORY

One family of genes allows cells to adapt to daily changes in environmental conditions by adjusting their internal "body clock," the circadian clock responsible for regular sleep-wake cycles. The new discovery by University of Tokyo scientists reveals for the first time that circadian regulation may be directly connected to cellular stress.

Circadian rhythms are found in almost all organisms with sensitivity to light. Problems with circadian rhythms in humans are related to diseases including high blood pressure (hypertension), metabolic disorders, and insomnia. Shift workers and the elderly both have increased risk for these diseases as a result of disruption of their circadian clock.

The research team responsible for the work is based at the University of Tokyo and led by Professor Yoshitaka Fukada and Assistant Professor Hikari Yoshitane in the Department of Biological Sciences. The latest results stem from a series of ongoing experiments and continue to build on the lab's interests in circadian studies. Collaborators led by Professor Hidenori Ichijo of the Graduate School of Pharmaceutical Sciences developed the unique mice used in the experiments.

Researchers used cells and mice that lacked three genes: apoptosis signal-regulating kinase 1, 2, and 3 (*Ask1*, *Ask2*, *Ask3*). In results from both cells and mice, the *Ask* genes were necessary to respond to both sudden changes to the environment and gradual changes over time.

Cells without the *Ask* genes did not show the changes to their circadian rhythm that are expected from normal cells growing in environments with too high or too low salt or sugar concentrations. The cells without *Ask* genes were also impervious to the changes expected after cells accumulate too much oxidative stress. Uncontrolled oxidative stress creates potentially toxic environments within cells due to changes in chemical balance.

"Many researchers in this field have long suspected oxidative stress and circadian rhythms are somehow connected because of the cycles of photosynthesis and DNA replication we see even in ancient organisms; photosynthesis requires sunlight and creates free radicals that could damage DNA, so cells postpone DNA replication and cell division until nighttime when photosynthesis has stopped. We are very excited about our results because we can approach the origin of the circadian clock by connecting oxidative stress and circadian regulation through the *Ask* genes," said Fukada.

The results in cells were further supported by observations of mouse behavior. Normal mice can change their wake-up time the next morning after unexpected light exposure during the night, as measured by their activity running on a wheel. Mice without *Ask* genes have less ability to synchronize their circadian clock to changes in environmental light-dark cycles.

"The dream is to have a tool to regulate circadian rhythms. Basic science like our research can show hints for later drug discovery work," said Yoshitane.

The University of Tokyo team plans to continue to study the detailed cellular mechanisms connecting Ask genes to oxidative stress and potential methods of influencing the circadian rhythm.

Story Source:

Materials provided by **University of Tokyo**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Kiyomichi Imamura, Hikari Yoshitane, Kazuki Hattori, Mitsuo Yamaguchi, Kento Yoshida, Takenori Okubo, Isao Naguro, Hidenori Ichijo, Yoshitaka Fukada. **ASK family kinases mediate cellular stress and redox signaling to circadian clock**. *Proceedings of the National Academy of Sciences*, 2018; 201719298 DOI: 10.1073/pnas.1719298115

目次に戻る

7. 空腹が慢性痛の認知を止める -マウス実験

2018 年 3 月 22 日

食べ物を見つけることは動物の生存スキルとして重要であるが、痛みを避けることも同様に重要である。ただ、痛みには価値があって、痛みがなければ、例えば、手を熱いコンロの上に置いたままにしてしまう可能性さえある。しかし、傷害後に起こる炎症性疼痛のように慢性的な痛みは、我々を衰弱させたり、重要な作業完了の妨げとなったりする。
今回ペンシルベニア大学の神経科学者らが *Cell* 誌に発表したマウス研究によって、脳には動物が空腹時に慢性痛を抑える働きがあることが示された。

英文記事：
https://www.eurekalert.org/pub_releases/2018-03/uop-bhs032018.php

---

PUBLIC RELEASE:22-MAR-2018

Being hungry shuts off perception of chronic pain

University of Pennsylvania

Pain can be valuable. Without it, we might let our hand linger on a hot stove, for example. But longer-lasting pain, such as the inflammatory pain that can arise after injury, can be debilitating and costly, preventing us from completing important tasks. In natural settings, the lethargy triggered by such pain could even hinder survival.

According to research by University of Pennsylvania neuroscientists, the brain has a way to suppress chronic pain when an animal is hungry, allowing it to go look for food while leaving intact the response to acute pain. Their work pinpointed a tiny population of 300 brain cells responsible for the ability to prioritize hunger over chronic pain, a group of neurons that may offer targets for novel pain therapies.

"In neuroscience we're very good about studying one behavior at a time," says J. Nicholas Betley, an assistant professor of biology in Penn's School of Arts and Sciences. "My lab studies hunger, and we can find neurons that make you hungry and manipulate those neurons and monitor their activity. But in the real world, things aren't that simple. You're not in an isolated situation where you're only hungry. This research was to try to understand how an animal integrates multiple needs to come to a behavioral conclusion that is optimal."

"We didn't set out having this expectation that hunger would influence pain sensation so significantly," says Alhadeff, "but when we saw these behaviors unfold before us, it made sense. If you're an animal, it doesn't matter if you have an injury, you need to be able to overcome that in order to go find the nutrients you need to survive."

The work will be published in the journal *Cell*. Betley and Alhadeff collaborated with Zhenwei Su, Elen Hernandez, Michelle L. Klima, and Sophie Z. Phillips of Penn Arts and Sciences; Ruby A. Holland and Bart C. De Jonghe of Penn's School of Nursing; and Caiying Guo and Adam W. Hantman of the Howard Hughes Medical Institute.

Betley's lab has focused on studying hunger, in particular how hunger can alter perception. Curious about how hunger may interact with the sensation of pain, the researchers observed how mice that hadn't eaten for 24 hours responded to either acute pain or longer-term inflammatory pain, which is thought to involve sensitization of neural circuits in the brain.

The Penn team found that hungry mice still responded to sources of acute pain but seemed less responsive to inflammatory pain than their well-fed counterparts. Their behavior was similar to that of mice that had been given an anti-inflammatory painkiller.

In a conditioning experiment, the researchers found that hungry mice did not avoid a place where they had been exposed to inflammatory pain, while mice that were not hungry avoided the place.

That left the question of what part of the brain was processing this intersection between hunger and pain. To find out, the researchers experimentally turned on a group of neurons known to be activated by hunger, agouti-related protein (AgRP) neurons, and found that chronic pain responses subsided, while acute pain responses stayed intact.

To get more specific about the brain region involved, the team next looked at which subpopulation of AgRP neurons appeared to integrate the signals of hunger with inflammatory pain. Activating each AgRP neuron subpopulation one at a time, Betley, Alhadeff, and colleagues found that stimulation of only a few hundred AgRP neurons that project to the parabrachial nucleus significantly suppressed inflammatory pain.

"It was really striking," Alhadeff says. "We showed that acute response to pain was perfectly intact, but inflammatory pain was suppressed to a very significant extent."

"The really interesting thing to my mind is that out of a brain of billions of neurons, this specific behavior is mediated by 300 or so neurons," Betley says.

Further experiments pinpointed the neurotransmitter, a molecule called NPY, responsible for selectively blocking inflammatory pain responses. Blocking receptors for NPY reversed the effects of hunger, and pain returned.

The researchers are excited by the potential clinical relevance of their findings. If they hold up in humans, this neural circuit offers a target for ameliorating the chronic pain that can linger after injuries, a type of pain that is currently often addressed by opioid medications, drugs that also inhibit acute pain.

"We don't want to shut off pain altogether," Alhadeff says, "there are adaptive reasons for pain, but it would be great to be able to target just the inflammatory pain."

Taking the next steps in this line of work, the researchers would like to map out in greater depth how the brain processes inflammatory pain, ideally identifying more targets for suppressing it. And they will continue considering how different survival behaviors integrate in the brain and how the brain processes and prioritizes them.

"We've initiated a new way of thinking about how behavior is prioritized," Betley says. "It's not that all the information is funneled up to your higher thinking centers in the brain but that there's

a hierarchy, a competition that occurs between different drives, that occurs before something like pain is even perceived."

###

The study was supported by Penn's School of Arts and Sciences, the American Heart Association, the Whitehall Foundation, and the National Institutes of Health (grants DG33400158, DK114104, DK731436, DK112561, and DK112812.)

目次に戻る

8. マウスの血管老化の原因を特定

2018 年 3 月 22 日

ハーバード大学医学部の科学者らは、マウスの血管老化、筋肉衰弱のメカニズムを明らかにし、3 月 22 日の *Cell* 誌で発表した。これによると、我々の年齢は動脈年齢に等しく、よって血管の老化を逆転させることで若々しい活力を回復させることができる、というものである。また、化学物質による治療は、血管の成長と筋肉の活力を回復させ、加齢による運動耐性を高める、としている。

研究チームは一連のマウス実験で、内皮細胞が SIRT1 として知られる重要なタンパク質を失い始めると血流の低下が生じることを発見した。以前の研究では SIRT1 が酵母やマウスにおいて老化を遅延させ寿命を延ばすことを示していたが、NAD+および SIRT1 が、血管壁や筋肉細胞の内皮細胞間の意思伝達を可能にする重要な界面を提供することを明らかにしている。

具体的には、SIRT1 欠損マウスが運動にどのように反応するかを観察したところ、SIRT1 欠損マウスの後肢筋肉は、SIRT1 を有する同年齢マウスと比べて、新生血管を形成する能力が著しく低下した、としている。

英文記事：

https://www.sciencedaily.com/releases/2018/03/180322141003.htm

---

Scientists pinpoint cause of vascular aging in mice

Treatment with chemical compound restored blood vessel growth and muscle vitality, boosted exercise endurance in aging animals

Date:

March 22, 2018

Source:

Harvard Medical School

Summary:

Scientists identify mechanism behind vascular aging, muscle demise in mice. Treatment with chemical compounds reversed vascular aging, stimulated blood vessel growth and blood flow, boosted exercise capacity in aging animals.

FULL STORY

Scientists have successfully restored blood vessel growth in aging animals.

Credit: Kevin Krull, for Harvard Medical School

We are as old as our arteries, the adage goes, so could reversing the aging of blood vessels hold the key to restoring youthful vitality?

The answer appears to be yes, at least in mice, according to a new study led by investigators at Harvard Medical School.

The research, published March 22 in *Cell*, identifies the key cellular mechanisms behind vascular aging and its effects on muscle health and has successfully reversed the process in animals.

The findings pinpoint a glitch in the normal crosstalk that occurs between muscles and blood vessels and keeps both tissues healthy.

Using the synthetic precursors of two molecules naturally present in the body, the scientists also managed to reverse blood vessel demise and muscle atrophy in aging mice, boosting their exercise endurance in the process.

The achievement, the team said, paves the way to identifying related therapies for humans.

"We've discovered a way to reverse vascular aging by boosting the presence of naturally occurring molecules in the body that augment the physiological response to exercise," said study senior investigator David Sinclair, professor in the Department of Genetics at Harvard Medical School and co-director of the Paul F. Glenn Center for the Biology of Aging at Harvard Medical School.

"The approach stimulates blood vessel growth and boosts stamina and endurance in mice and sets the stage for therapies in humans to address the spectrum of diseases that arise from vascular aging," added Sinclair, who is also a professor at the University of New South Wales School of Medical Sciences in Sydney, Australia.

The researchers caution that many promising treatments in mice don't have the same effect in humans due to critical differences in biology. However, the results of the experiments were dramatic enough to prompt the research team to pursue experiments in humans. Clinical trials for safety are already under way, Sinclair said.

As old as our blood vessels

Sinclair and team set out to unravel the mechanisms behind one of biology's inevitabilities: aging.

As we grow old, we become weak and frail. A constellation of physiological changes -- some subtle, some dramatic -- precipitate this inevitable decline. What exactly happens inside our cells to cause the biological shifts that lead to aging? It's a question that has vexed Sinclair and team for years.

As we age, our tiniest blood vessels wither and die, causing reduced blood flow and compromised oxygenation of organs and tissues. Vascular aging is responsible for a constellation of disorders, such as cardiac and neurologic conditions, muscle loss, impaired wound healing and overall frailty, among others. Scientists have known that loss of blood flow to organs and tissues leads to the

build-up of toxins and low oxygen levels. The so-called endothelial cells, which line blood vessels, are essential for the health and growth of blood vessels that supply oxygen-rich and nutrient-loaded blood to organs and tissues. But as these endothelial cells age, blood vessels atrophy, new blood vessels fail to form and blood flow to most parts of the body gradually diminishes. This dynamic is particularly striking in muscles, which are heavily vascularized and rely on robust blood supply to function.

Muscles begin to shrivel and grow weaker with age, a condition known as sarcopenia. The process can be slowed down with regular exercise, but gradually even exercise becomes less effective at holding off this weakening.

Sinclair and team wondered: What precisely curtails the blood flow and precipitates this unavoidable decline? Why does even exercise lose its protective power to sustain muscle vitality? Is this process reversible?

In a series of experiments, the team found that reduced blood flow develops as endothelial cells start to lose a critical protein known as sirtuin1, or SIRT1. Previous studies have shown that SIRT1 delays aging and extends life in yeast and mice.

SIRT1 loss is, in turn, precipitated by the loss of NAD+, a key regulator of protein interactions and DNA repair that was identified more than a century ago. Previous research by Sinclair and others has shown that NAD+, which also declines with age, boosts the activity of SIRT1.

A stimulating conversation

The study reveals that NAD+ and SIRT1 provide a critical interface that enables the conversation between endothelial cells in the walls of blood vessels and muscle cells.

Specifically, the experiments reveal that in young mouse muscle, SIRT1 signaling is activated and generates new capillaries, the tiniest blood vessels in the body that supply oxygen and nutrients to tissues and organs. However, as NAD+/SIRT1 activity diminishes over time, the study found, so does the blood flow, leaving muscle tissue nutrient-deprived and oxygen-starved.

Indeed, when researchers deleted SIRT1 in the endothelial cells of young mice, they observed markedly diminished capillary density and decreased number of capillaries, compared with mice that had intact SIRT1. Mice whose endothelial cells lacked SIRT1 had poor exercise tolerance, managing to run only half the distance covered by their SIRT1-intact peers.

To determine SIRT1's role in exercise-induced blood vessel growth, the researchers observed how SIRT1-deficient mice responded to exercise. After a month-long training regimen, the hind-leg muscles of SIRT1-deficient mice showed markedly diminished ability to form new blood vessels in response to exercise compared with same-age mice that had intact SIRT1 in their endothelial cells.

Exercise-induced blood vessel formation is known to occur in response to growth-stimulating proteins released by muscles under strain. SIRT1, however, appears to be the key messenger relaying growth-factor signaling from muscles to blood vessels, the study found.

Experiments showed that endothelial cells lacking SIRT1 were desensitized to the growth-stimulating proteins released by exercised muscles.

"It's as if these cells had grown deaf to the signals that muscles sent their way," Sinclair said.

The observation, he added, explains why age-related loss of SIRT1 leads to muscle atrophy and blood vessel demise.

Since the experiments revealed the critical role of SIRT1 in exercise-induced blood vessel formation, the researchers wondered whether boosting SIRT1 levels would stimulate blood vessel growth and stave off muscle wasting.

Exercise in a pill?

The scientists set their sights on NAD+, a molecule conserved across many life forms, known to decline with age and previously shown to stimulate SIRT1 activity.

"We reasoned that declining NAD+ levels reduce SIRT1 activity and thus interfere with aging mice's ability to grow new blood vessels," said study first author Abhirup Das, who conducted the work as a post-doctoral fellow in Sinclair's lab, currently a visiting scholar in genetics at Harvard Medical School and a post-doctoral research fellow at the University of South New Wales School of Medical Sciences.

To test this premise, scientists used a chemical compound called NMN, a NAD+ precursor, previously shown to play a role in repairing cellular DNA and maintaining cell vitality.

In lab dish experiments, endothelial cells from humans and mice treated with NMN showed enhanced growth capacity and reduced cell death.

Next, the team gave NMN over two months to a group of mice that were 20 months old -- the rough equivalent of 70 in human years. NMN treatment restored the number of blood capillaries and

capillary density to those seen in younger mice. Blood flow to the muscles also increased and was significantly higher than blood supply to the muscles seen in same-age mice that didn't receive NMN.

The most striking effect, however, emerged in the aging mice's ability to exercise. These animals showed between 56 and 80 percent greater exercise capacity, compared with untreated mice the study showed. The NMN-treated animals managed to run 430 meters, or about 1,400 feet, on average, compared with 240 meters, or 780 feet, on average, for their untreated peers.

To see whether the effects of NMN could be further augmented, the researchers added a second compound to the treatment regimen. The compound, sodium hydrosulfide (NaHS), is a precursor to hydrogen sulfide, which also boosts the activity of SIRT1.

A group of 32-month-old mice -- the rough equivalent to 90 in human years -- receiving the combo treatment for four weeks were able to run, on average, twice as long as untreated mice. In comparison, mice treated with NMN alone ran 1.6 times farther, on average, than untreated animals.

"These are really old mice so our finding that the combo treatment doubles their running capacity is nothing short of intriguing," said study co-author James Mitchell, associate professor of genetics and complex diseases at the Harvard T. H. Chan School of Public Health. Research led by Mitchell and published in the same issue of Cell also found sodium hydrosulfide to augment blood vessel formation in the muscles of mice.

Interestingly, the NMN treatment did not improve blood vessel density and exercise capacity in young sedentary mice. However, it did boost blood vessel formation and exercise capacity in young mice that had been exercising regularly for a month.

"This observation underscores the notion that age plays a critical role in the crosstalk between blood vessels and muscles and points to a loss of NAD+ and SIRT1 as the reason behind loss of exercise effectiveness after middle age," Das said.

The researchers say their findings may pave the way to therapeutic advances that hold promise for the millions of older people for whom regular physical activity is not an option.

"Even if you're an athlete, you eventually decline," Sinclair said. "But there is another category of people -- what about those who are in a wheelchair or those with otherwise reduced mobility?"

The team's ultimate goal is to replicate the findings and, eventually, move toward developing small-molecule, NMN-based drugs that mimic the effects of exercise -- enhanced blood flow and oxygenation of muscles and other tissues. Such therapies may even help with new vessel growth of organs that suffer tissue-damaging loss of blood supply and oxygen, a common scenario in heart attacks and ischemic strokes, the team said.

Neo-vascularization -- the formation of new blood vessels -- should be treated with caution, the researchers say, because increased blood supply could inadvertently fuel tumor growth.

"The last thing you want to do is provide extra blood and nourishment to a tumor if you already have one," said study co-author Lindsay Wu, at the University of New South Wales School of Medical Sciences.

Sinclair and Wu point out that experiments done as part of the current study provide no evidence that treatment with NMN stimulated tumor development in animals treated with the compound.

Story Source:

Materials provided by **Harvard Medical School**. Original written by Ekaterina Pesheva. *Note: Content may be edited for style and length.*

Journal Reference:

1. Abhirup Das, George X. Huang, Michael S. Bonkowski, Alban Longchamp, Catherine Li, Michael B. Schultz, Lynn-Jee Kim, Brenna Osborne, Sanket Joshi, Yuancheng Lu, Jose Humberto Treviño-Villarreal, Myung-Jin Kang, Tzong-tyng Hung, Brendan Lee, Eric O. Williams, Masaki Igarashi, James R. Mitchell, Lindsay E. Wu, Nigel Turner, Zolt Arany, Leonard Guarente, David A. Sinclair. **Impairment of an Endothelial NAD -H 2 S Signaling Network Is a Reversible Cause of Vascular Aging**. *Cell*, 2018; 173 (1): 74 DOI: 10.1016/j.cell.2018.02.008

Cite This Page:

- MLA
- APA
- Chicago

Harvard Medical School. "Scientists pinpoint cause of vascular aging in mice: Treatment with chemical compound restored blood vessel growth and muscle vitality, boosted exercise endurance in aging animals." ScienceDaily. ScienceDaily, 22 March 2018. <www.sciencedaily.com/releases/2018/03/180322141003.htm>.

目次に戻る

9．超薄型内視鏡が脳深部で発射するニューロンをとらえる -マウス実験

2018 年 3 月 26 日

生存するマウスの脳におけるニューロンの活動を画像化することができる超薄型の内視鏡が開発された。
このデバイスを開発したのは、マサチューセッツ工科大学のポスドク研究員の Shay Ohayon 氏で、人間の髪の毛ほど薄いこの内視鏡は脳の深部にまで到達することができ、顕微鏡や他の種類の内視鏡では見えない領域に研究者がアクセスできるようになる、としている。
このマイクロ内視鏡の 1 つの限界は、ファイバーの曲がりが画像を生成する能力を失わせることであり、この曲がり問題が解決されるとこのデバイスの用途が大幅に拡大する。そこで既に多くの研究グループがこの問題に取り組んでいる、とのことである。

英文記事：
https://www.sciencedaily.com/releases/2018/03/180326110031.htm

---

Ultrathin endoscope captures neurons firing deep in the brain

New fiber-based endoscope, tested in mice, poised to bring new insights into brain function

Date:

March 26, 2018

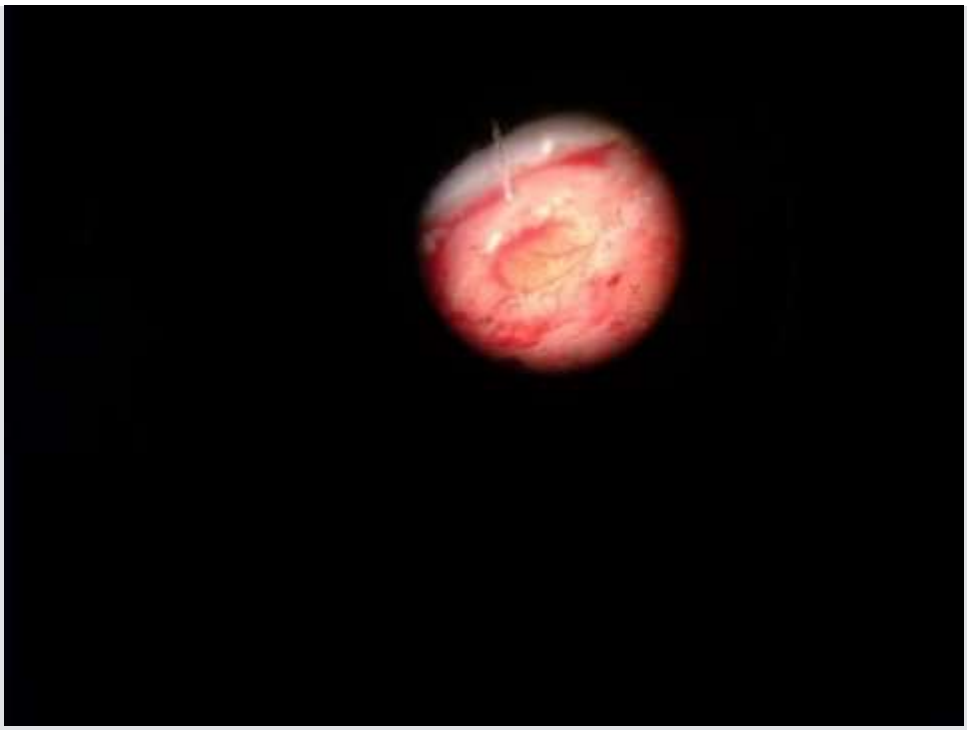
Source:

The Optical Society

Summary:

Researchers have developed an endoscope as thin as a human hair that can image the activity of neurons in the brains of living mice, giving researchers access to areas that cannot be seen with microscopes or other types of endoscopes.

FULL STORY



A new endoscope as small as a human hair was used to image neuronal activity in mice. The optical fiber microendoscope (upper left) is shown just before it is inserted into tissue.

Credit: Shay Ohayon, Massachusetts Institute of Technology

Researchers have developed an endoscope as thin as a human hair that can image the activity of neurons in the brains of living mice. Because it is so thin, the endoscope can reach deep into the brain, giving researchers access to areas that cannot be seen with microscopes or other types of endoscopes.

"In addition to being used in animal studies to help us understand how the brain works, this new endoscope might one day be useful for certain applications in people," said Shay Ohayon, who developed the device as a postdoctoral researcher in James DiCarlo's lab at the Massachusetts Institute of Technology. "It could offer a smaller, and thus more comfortable, instrument for imaging within the nasal cavity, for example."

The new endoscope is based on an optical fiber just 125 microns thick. Because the device is five to ten times thinner than the smallest commercially available microendoscopes, it can be pushed deeper into the brain tissue without causing significant damage.

In The Optical Society (OSA) journal *Biomedical Optics Express*, the researchers report that the endoscope can capture micron-scale resolution images of neurons firing. This is the first time that imaging with such a thin endoscope has been demonstrated in a living animal.

"With further development, the new microendoscope could be used to image neuron activity in previously inaccessible parts of the brain such as the visual cortex of primate animal models," said Ohayon. "It might also be used to study how neurons from different regions of the brain communicate with each other."

Acquiring images from a fiber

The new microendoscope is based on a multimode optical fiber, which can carry different multiple beams of light at the same time. When light enters the fiber, it can be manipulated to generate a tiny spot at the other end, and can be moved to different positions on the tissue without moving the fiber. Scanning the tiny spot across the sample allows it to excite fluorescent molecules used to label neuron activity. As the fluorescence from each spot travels back through the fiber, an image of neuron activity is formed.

"To achieve scanning fast enough to image neurons firing, we used an optical component known as a digital mirror device (DMD) to quickly move the light spot," said Ohayon. "We developed a technique that allowed us to use the DMD to scan light at speeds up to 20 kilohertz, which is fast enough to see fluorescence from active neurons."

Because the multimode fibers used for the endoscope scramble light, the researchers applied a method called wavefront shaping to convert the scrambled light into images. For wavefront shaping, they sent various patterns of light through the fiber to a camera at the other end and recorded exactly how that specific fiber changed light that passed through. The camera was then removed, and the fiber placed into the brain for imaging. The previously obtained information

about how the fiber changes the light is then used to generate and scan a small point across the field of view.

Imaging living neurons

After successfully imaging cultured cells, the researchers tested their microendoscope on anesthetized mice. They inserted the fiber through a tiny hole in the skull of a mouse and slowly lowered it into the brain. To image the neurons firing, the researchers used a technique called calcium imaging that creates fluorescence in response to the influx of calcium that occurs when a neuron fires.

"One of the advantages of using an endoscope so thin is that as you lower it into the brain, you can see all the blood vessels and navigate the fiber to avoid hitting them," said Ohayon.

In addition to showing that their endoscope could catch detailed neuronal activity the researchers also demonstrated that multiple colors of light could be used for imaging. This capability could be used to observe interactions between two groups of neurons each labeled with a different color, for example.

For standard imaging, the endoscope images the neurons at the very tip of the fiber. However, the researchers also showed that the microendoscope could image up to about 100 microns away from the tip. "This is very useful because when the fiber is inserted into the brain, it may affect the function of neurons very close to the fiber," explained Ohayon. "Imaging an area slightly away from the fiber makes it easier to capture healthy neurons."

Dealing with bends in the fiber

One limitation of the microendoscope is that any bends in the fiber cause it to lose the ability to produce images. Although this didn't affect the experiments described in the paper because the fiber was kept straight as it was pushed into the brain, solving the bending problem could greatly expand the applications for the device. Various research groups are working on new types of fibers that are less susceptible to bending and computational methods that might compensate for bending in real-time.

"If this bending problem can be solved, it will likely change the way endoscopy in people is performed by allowing much thinner probes to be used," said Ohayon. "This would allow more comfortable imaging than today's large endoscopes and may enable imaging in parts of the body that aren't currently feasible."

Story Source:

Materials provided by **The Optical Society**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Shay Ohayon, Antonio Caravaca-Aguirre, Rafael Piestun, James J. DiCarlo. **Minimally invasive multimode optical fiber microendoscope for deep brain fluorescence imaging**. *Biomedical Optics Express*, 2018; 9 (4): 1492 DOI: 10.1364/BOE.9.001492

Cite This Page:

- MLA
- APA
- Chicago

The Optical Society. "Ultrathin endoscope captures neurons firing deep in the brain: New fiber-based endoscope, tested in mice, poised to bring new insights into brain function." ScienceDaily. ScienceDaily, 26 March 2018. <www.sciencedaily.com/releases/2018/03/180326110031.htm>.

目次に戻る

10. ハンティントン病のブタモデル -マウスモデルとの比較

2018 年 3 月 29 日

エモリー大学医学部の研究者らは、済南大学および広州中国科学アカデミーと共同で、ハンティントン病（HD）のブタモデルの作成に成功した。この研究は 3 月 29 日に *Cell* 誌に掲載される。

エモリー大学医学部人間遺伝学科の Xiao-Jiang Li 教授は、遺伝子改変されたマウスが神経変性疾患のモデル化のために広く使用されているものの、マウスモデルはヒトの脳に見られる典型的な神経変性あるいは顕著な神経細胞喪失を欠いているのに対して、ブタモデルは神経変性のパターンが人間とほぼ同じであるため、マウスモデルよりも良好に試験することができる、と言っている。また、ブタがマウスと比べてサイズ的にヒトに近く、ブタの HD モデルは、大きな動物モデルがアルツハイマー病、パーキンソン病および ALS（筋委縮性側索硬化症）など他の神経変性疾患をより良くモデル化できることを示唆する例である、としている。

ちなみに、Li 研究室は昨年、CRISPR-Cas9 遺伝子編集によってマウスモデルが HD の徴候を逆転できることを *Journal of Clinical Investigation* 誌で発表、またトランスジェニック HD サルモデルも作成している。

英文記事：

www.sciencenewsline.com/news/20180329195700022.html

Pig Model of Huntington's Offers Advantages for Testing Treatments

Published: March 29, 2018.
Released by Emory Health Sciences

Go to mobile page.

Using genetic engineering technology, a team of scientists has established a pig model of Huntington's disease (HD), an inherited neurodegenerative disease. The researchers anticipate that the pigs could be a practical way to test treatments for HD, which is caused by a gene encoding a toxic protein that causes brain cells to die.

The research is scheduled for publication in *Cell* on March 29th.

Although genetically modified mice have been used widely to model neurodegenerative diseases, they lack the typical neurodegeneration or overt neuronal loss seen in human brains, says corresponding author Xiao-Jiang Li, MD, PhD, distinguished professor of human genetics at Emory University School of Medicine.

The pig HD model is an example that suggests large animal models could better model other neurodegenerative diseases, such as Alzheimer's, Parkinson's and ALS (amyotrophic lateral sclerosis), he says. A HD pig could be an opportunity to test if CRISPR-Cas9 gene editing can work in larger animals before clinical applications in humans.

In comparison with mice, delivery of treatments to affected nervous system tissues can be better tested in pigs, because their size is closer to that of humans. The pig model of HD also more closely matches the symptoms of the human disease. Compared with non-human primate models, the pigs offer advantages of faster breeding and larger litter sizes, the researchers say.

The pig model of HD was established by researchers at Emory University School of Medicine, together with colleagues at Jinan University and Chinese Academy of Sciences in Guangzhou.

"We think the pig model will fill an important gap," says co-senior author Shihua Li, M.D, professor of human genetics at Emory University School of Medicine. "In pigs, the pattern of

neurodegeneration is almost the same as in humans, and there have been several treatments tested in mouse models that didn't translate to human."

Shihua and Xiao-Jiang Li jointly run a lab at Emory, which collaborated with Liangxue Lai, PhD, associate director of the South China Institute of Stem Cells and Regeneration Medicine, Chinese Academy of Sciences. The lead author of the paper is Sen Yan at Jinan University's Guangdong-Hongkong-Macau Institute of CNS Regeneration. Yan was trained in the Li Lab as a visiting PhD student at Emory. The pigs are housed in Guangzhou.

Symptoms displayed by the genetically altered pigs include movement problems. They show respiratory difficulties, which resemble those experienced by humans with HD and are not seen in mouse models of HD. In addition, the pigs show degeneration of the striatum, the region of the brain most affected by HD in humans, more than other regions of the brain.

Huntington's disease is caused by a gene encoding a toxic protein (mutant huntingtin or mHTT). mHTT contains abnormally long repeats of a single amino acid, glutamine. Symptoms commonly appear in mid-life and include uncontrolled movements, mood swings and cognitive decline.

Researchers used the CRISPR/Cas9 gene editing technique to introduce a segment of a human gene causing Huntington's, with a very long glutamine repeat region, into pig fibroblast cells. Then somatic cell nuclear transfer generated pig embryos carrying this genetic alteration. The alteration is referred to a "knock in" because the changed gene is in its natural context.

Last year, the Li lab published a paper in *Journal of Clinical Investigation* showing that CRISPR-Cas9 gene editing, delivered by viral vector, can reverse signs of HD in a mouse model. Working with Liangxue Lai, the Li lab has generated transgenic -- not "knock-in" -- pigs that are models for HD. The Li lab also collaborated with Anthony Chan, DVM, PhD at Yerkes National Primate Research Center to generate a transgenic HD monkey model.

Journal reference: dx.doi.org/10.1016/j.cell.2018.03.005

The above story is based on materials provided by Emory Health Sciences.